

空洞型肺结核的相关研究进展

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摘 要

肺空洞是结核病(TB)中最常见的临床特征之一。有大量文献对空洞型肺结核相关的潜在危险因素进行研究, 本文就目前提出的一些潜在危险因素进行综述。根据本文中总结, DM (糖尿病)、结核分枝杆菌(MTB)载量、结核分枝杆菌(MTB)的耐药性以及吸烟作为空洞型肺结核疾病的潜在危险因素, 与结核性空洞的发生、发展相互关联, 互相影响。随着对空洞型肺结核临床相关因素的研究不断地深入, 使我们能够确定导致空洞疾病风险增加的分子因素, 让我们可以通过对早期存在危险因素的人群进行干预, 以降低空洞型肺结核的发病率。

关键词

空洞型肺结核, 肺结核, 糖尿病, 细菌载量, 耐药性结核, 吸烟与肺结核

Research Progress of Cavitory Pulmonary Tuberculosis

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Abstract

Pulmonary cavity is one of the most common clinical features of tuberculosis. There are a large number of literatures on the potential risk factors related to cavitory pulmonary tuberculosis. This article reviews some potential risk factors proposed at present. According to the summary in this article, DM (diabetes), bacterial load, drug resistance of tuberculosis bacteria and smoking, as potential risk factors of cavitory pulmonary tuberculosis disease, are related to and affect the occurrence and development of tuberculous cavities. With the continuous deepening of the research

on clinical related factors of cavitory pulmonary tuberculosis, we can determine the molecular factors that lead to the increased risk of cavitory disease, so that we can reduce the incidence rate of cavitory pulmonary tuberculosis by intervening the population with early risk factors.

Keywords

Cavity Type Pulmonary Tuberculosis, Pulmonary Tuberculosis, Diabetes, Bacterial Load, Drug-Resistant Tuberculosis, Smoking and Pulmonary Tuberculosis

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1. 引言

结核病(Tuberculosis, 简称 TB)一直是一个严重的公共卫生问题, 2022 年 WHO (世界卫生组织)发布的《2022 年全球结核病报告》中表示我国 2021 年的初治结核病人数量约为 78.0 万(2020 年 84.2 万), 结核病发病率约为 55/10 万(2020 年 59/10 万)。在全球 30 个结核病高负担国家中我国结核病发病数排第 3 位, 仅次于印度尼西亚(96.9 万)和印度(295 万) [1]。而空洞性肺结核又是活动性肺结核最常见的影像学表现, 是由干酪样坏死组织液化并经气道排出所致。空洞是肺结核的一种危险表现, 与不良结果、高复发率、高传播率和耐药性的发展有关[2] [3]。空洞性肺结核具有病程长、痰菌阳性时间长、合并支气管结核、传染性高、空腔闭合困难、治疗效果不佳、复发率高等特点。应用常规化疗药物治疗药物不易进入腔内, 难以达到有效浓度[2] [4]。然而, 在抗生素时代, 空洞往往被认为是治疗失败的最极端结果, 也是结核病研究最少的方面之一。现就空洞型肺结核形成的危险因素的相关性研究进行综述。

2. 糖尿病与空洞型肺结核

国际糖尿病联合会(International Federation of diabetes)估计, 2019 年全球糖尿流行率估计为 9.3% (4.63 亿人), 到 2030 年上升至 10.2% (5.78 亿人)和 2045 年上升至 10.9% (7 亿人) [5]。糖尿病和结核病之间的联系已经有几个世纪了[6], Restrepo BI 在报告中总结到, 在 20 世纪 50 年代, 没有死于糖尿病的糖尿病患者很可能死于结核病[7]。随着糖尿病用胰岛素和治疗结核病的抗生素的出现, 这种联系减少了, 但在 20 世纪 80 年代, 由于糖尿病“大流行”, 这种共存现象开始重新出现, 预计到 2030 年将达到 4.39 亿患者, 主要归因于 2 型糖尿病[8]。因此, 世界卫生组织已将糖尿病确定为一个被忽视的、重要的和重新出现的结核病危险因素[7]。

在这篇综述中, “糖尿病”主要指的是 2 型糖尿病, 因为它是最普遍的形式。几项研究报告表明与没有糖尿病(DM)的肺结核(TB)患者相比, 患有糖尿病(DM)的肺结核(TB)患者出现空洞的频率更高[9]-[17]。Perez Guzman 报告称, 仅在肺结核(TB)患者中, 空洞随着年龄的增长而变得不那么常见, 而在所有年龄段的糖尿病(DM)患者中空洞的发生率仍然很高[18]。而另一项研究却认为在 35~44 岁的人群中, 空洞性病患者的比例最高, 并且随着年龄的增长而逐渐减少, 糖尿病(DM)并没有掩盖老年人和年轻人之间空洞病变的不同风险, 反而加剧了这种风险[19]。Chiang C-Y 的研究表明了糖尿病(DM)增加了空洞病变的风险, 尤其是在年轻患者中更甚, 且糖尿病(DM)患者肺部出现空洞的风险是由血糖控制驱动的, 血糖控制不佳的患者肺部空洞形成的概率大大增加[19]。血糖控制不佳的糖尿病(DM)患者肺部空洞病变的频率增加可能与 Th1 相关细胞因子的表达减少有关[14] [20] [21] [22], 所以适当的血糖控制不仅可以降低糖尿

病(DM)患者患结核病(TB)的风险, 还可以降低糖尿病(DM)病人患肺结核(TB)空洞病变的风险[19]。

3. 结核分枝杆菌(MTB)载量与空洞型肺结核

空洞型肺结核是结核病中最常观察到的临床特征之一, 在诊断时占成人肺结核患者的 40%以上[23] [24] [25], 有发现表明, 结核空洞腔壁中的结核分枝杆菌(MTB)的细菌载量是干酪坏死的 105 倍[23] [26]。多项实验室检查也表明, 空洞与痰液中结核分枝杆菌(MTB)载量较高有关, 可能因为腔内的高氧浓度有利于细菌的复制并增加痰液中的结核分枝杆菌(MTB)负荷[27] [28]。同时因为这些空洞的腔壁存在, 屏障的作用使之降低了空洞内血药的浓度, 导致空洞内细菌载量高, 增加了空洞的危险性[29]。这可能是早期治疗的有力指标[26] [27] [28], 另几项使用定性涂片和培养的研究也证实了这一点[27] [28] [30] [31]。

在早期的组织病理学研究中, Lowenstein Jensen 斜面上的半定量读数显示结核腔的内部坏死区和软化干酪样物质含有更多的结核杆菌, 大大超过闭合性病变[31]。一项定量研究证明, 在纳入研究的病例中, 有 80%的闭合腔每倾斜斜面上半定量读数有 > 200 个菌落, 而只有 22%的闭合病变有相同数量[24]。尽管由于研究方法上的差异, 我们不能直接对这些研究进行比较, 但最终的结果证实了早期的组织学和细菌学研究。同时作者还比较了初始胸片上疾病的程度和空洞病的存在与细菌负荷的关系, 在空洞组和非空洞组中, 细菌负荷随着疾病的影像学严重程度而增加, 但无论疾病类别的程度怎么发展, 空洞患者的痰标本都有较高的 CFU (菌落形成单位)计数[24]。这些研究都表明空洞性病变患者的结核杆菌数量远高于非空洞性患者。

4. 耐药性与空洞型肺结核

耐药结核病(MDR-TB)的持续蔓延是全球结核病控制面临的最紧迫和最困难的挑战之一[32]。结核分枝杆菌(MTB)的多重耐药性是空洞型肺结核相关的另一个重要因素[33]。在耐多药病例中, 结核杆菌对抗结核药物产生耐药性, 导致慢性进展性疾病, 继而使患者肺部出现空洞[34]。而之前的一项研究中提到, 肺部空洞的存在与治疗期间耐药性的发展有关[33]。因此, 肺空洞与耐药之间存在相互作用的关系, 这可能会加速肺空洞的产生和扩大。

空洞是肺结核患者常见的影像征象, 被认为是活动性结核的影像学表现之一[35]。以往有文献对耐药结核病(MDR-TB)的影像学研究来看, 耐药结核病(MDR-TB)的常见影像学有小叶中心小结节、分支线状和结节状混浊(树芽征)、斑片状或小叶状实变区、空洞和支气管扩张等征象, 与继发性肺结核具有相似的影像学特征[36]。但是耐药结核病(MDR-TB)却更容易出现结节、空洞、支气管扩张等慢性病程的影像学表现[37] [38]。国内外多数文献报道认为耐药结核病(MDR-TB)与厚壁、多发、较大空洞相关, 虽然存在敏感度低的问题, 但如果空洞数量 ≥ 3 个, 空洞直径 ≥ 30 mm, 对 MDR-TB 诊断的特异度相对较高[37] [39] [40] [41]。

5. 吸烟与空洞型肺结核

烟草使用是一个重大的公共卫生问题, 也是一个重要的可预防的过早死亡风险[42], 大量的研究已证明吸烟与结核病之间存在关联[43] [44], 并发现吸烟者死于结核病的风险增加[45]。Janah Hicham 在文中总结出烟草烟雾通过多种机制促进结核分枝杆菌感染: 分别是粘膜纤毛清除受、肺泡巨噬细胞性能下降、肺淋巴细胞免疫抑制、自然杀伤细胞的细胞毒活性降低、肺树突状细胞[46]。也有研究表明吸烟会引起呼吸系统中许多病理生理学变化, 包括免疫效应、清除率降低和吸入病原体粘附性改变[47], 吸烟还通过抑制固有免疫激活和肺 T 细胞募集来阻碍抗结核 T 辅助因子 1 型(Th-1)免疫的肺部表达[48]。Altet-Gómez 在研究中证实吸烟者更容易患上更多的肺部疾病(aOR 1.5)和更多的空洞病变(aOR 1.9), 并且更有可能需

要住院治疗(aOR 1.8), 而且住院时间更长[49]。一项研究表明, 吸烟者和前吸烟者与不吸烟者之间相比, 在治疗完成后胸部 X 光显示空洞清除率降低[46]。

6. 小结与展望

空洞型肺结核具有病程长、病灶迁延不愈、治疗效果差、传染性强等特点, 对人体的消耗极大, 患者体质通常较差, 空洞病灶导致结核杆菌在肺内传播, 使病情进展迅速, 进一步破坏患者肺组织, 严重影响患者肺功能。同时因为病情反复的可能性大, 给患者本身、家庭乃至社会带来了严重的负担和经济压力。通过上述总结, 我们认识到了 DM、细菌载量、结核杆菌耐药性及吸烟与空洞型肺结核之间密切的关系, 他们相互影响, 相互作用, 使疾病进展更快, 更甚者威胁患者生命。相信在对空洞型肺结核的相关临床因素的不断研究下, 我们可以更清楚地认识到其中的危险因素, 早期为存在危险因素的患者进行临床干预, 为临床工作中预防空洞的形成以及疾病的进展提供了便利。

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